PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Stabilized Phenothiazine Preparations

We, SMITH KLINE & FRENCH LABORATORIES, a corporation organized under the laws of the Commonwealth of Pennsylvania, one of the United States of America, of 1530, Spring Garden Street, Philadelphia, Commonwealth of Pennsylvania, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

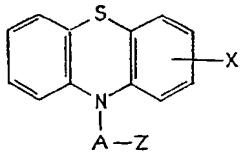
This invention relates to light-stable phenothiazine preparations and the method of making said preparations. More specifically, this invention relates to phenothiazine preparations stabilized to light by the presence of saccharin or a soluble saccharin salt.

Light such as ordinary daylight causes the phenothiazine nucleus to decompose and change color at a substantial rate. The potency and color of compounds containing a phenothiazine nucleus are in this manner materially affected. This is a marked deficiency in these compounds which have a wider variety of uses and is particularly troublesome in the medicinal and veterinary fields where they are widely employed variously as antiemetics tranquilizers, sedatives, antihistaminics, antispasmodics and anthelmintics for cattle or for delicing poultry. The problem is particularly acute when the compound containing the phenothiazine nucleus is in an aqueous solution or otherwise exposed to a substantial amount of moisture as in wet granulation tabletting.

This problem has now been solved by the present invention which comprises a preparation containing, as its essential ingredients, a compound containing a phenothiazine nucleus (hereinafter referred to in the specification and claims as a "phenothiazine nucleus compound") and saccharin or, preferably, a soluble saccharin salt for instance an ammonium, magnesium, calcium or alkali metal salt such as the sodium or potassium salt in an amount sufficient to light-stabilize the phenothiazine nucleus compound. The soluble salts are preferred for use in aqueous preparations and advantageously should be as soluble in water as saccharin itself.

The proportion of the phenothiazine nucleus compound to saccharin may vary from 1:1 to 1000:1, advantageously from 5:1 to 500:1. Only a very small amount of the saccharin component is necessary to exert a substantial light stabilizing influence on the phenothiazine nucleus compound.

The phenothiazine nucleus compound, for example, can be phenothiazine or a substituted phenothiazine such as 10-aminoalkylphenothiazines optionally substituted in a benzenoid ring of the nucleus. Such substituted phenothiazine compounds are exemplified by the therapeutically effective compounds variously having tranquilizing, antiemetic, sedative, antihistaminic, antispasdomic and anthelmintic activity and having the following general formula:



when:

X is a simple moiety such as hydrogen, halogen, lower alkyl, lower alkoxy, carbalkoxy, di-lower-alkyl-sulfamyl, lower alkylthio, trifluoromethyl or lower alkanoyl such as acetyl;

A is a straight or branched lower alkylene chain separating the nitrogen atom to which it is attached from the basic terminal group Z by at least 2 carbons;

Z is a basic terminal group, for example, di-lower-alkylamino such as dimethylamino, diethylamino or dibutylamino or a five to seven-membered heterocyclic amino group such as N-lower-alkylpiperazinyl such as N-methylpiperazinyl or N-propylpiperazinyl, nortropinyl, piperadinyl, N-lower-alkylpiperidinyl such as N-methylpiperidinyl or N-propyl-

[*Price 3s. 6d.*]

piperidinyl, N-hydroxy-lower-alkylpiperazinyl such as N - hydroxypropylpiperazinyl, N-hydroxyethylpiperazinyl, N - hydroxy - lower-alkoxy - lower - alkylpiperazinyl such as N-hydroxypropoxypropylpiperazinyl or N - hydroxyethoxyethylpiperazinyl or N - lower-alkanoyloxy-lower-alkylpiperazinyl such as N-acetoxybutylpiperazinyl or N - acetoxyethylpiperazinyl.

Where the term "lower" is used to modify a group, it is meant that the group has from 1 to 6 carbon atoms.

The phenothiazine nucleus compound of the light-stable combination of this invention is preferably chlorpromazine, promazine, prochloroperazine, perphenazine, trimeprazine, methotrimeprazine, mepazine, ethpropazine, acetylperphenazine, methylpromazine, triphentizine (trifluopromazine), trifluoperazine, ethotrimeprazine, methopromazine, acetylpromazine or diethazine.

The phenothiazine nucleus compound, if it is substituted by a basic aminoalkyl side chain, may also be any pharmaceutically-acceptable, nontoxic acid addition salt of the above bases, such as a salt with an organic acid, such as the tartrate, maleate or ethanedisulfonate or a salt with an inorganic acid, such as the hydrochloride, phosphate, hydrobromide or sulfate. When such salts are present in aqueous solution, it is often desirable to buffer the solution by adding substances the anion of which is the same as the anion present in the salt.

The preparation of this invention can be in the form of a simple mixture of the essential ingredients or can contain other ingredients, for example, diluents or carriers such as, for example, water.

Where a therapeutically effective phenothiazine nucleus compound is employed, the preparation of this invention can be in a suitable pharmaceutical form such as a tablet or a hard gelatin capsule with the essential ingredients admixed with a pharmaceutical carrier or diluent such as starch, talc, lactose, stearic acid or gelatin. Numerous other pharmaceutical forms can be employed, for example, the essential ingredients can be in a liquid carrier such as water, peanut oil or olive oil and, if desired, placed in a soft gelatin capsule.

The preferred pharmaceutical form is an aqueous solution for oral or parenteral use. Whether for oral or parenteral use, conventional pharmaceutical additives can be employed. Thus, for example, a parenteral preparation may contain preservatives such as benzyl alcohol or methyl p-hydroxybenzoate, buffering agents and salts to bring the injectable preparation to a satisfactory pH, or other stabilizing agents such as ascorbic acid or sodium bisulfite. Similarly, an oral preparation may contain stabilizing agents such as antioxidants.

In a pharmaceutical preparation, the phenothiazine nucleus compound may be present in any proportions desired by the dosage requirement of the final product, considering in the case of aqueous preparations, the limitations of solubility. The amount of the therapeutically effective phenothiazine nucleus compound advantageously will be from 0.1 to 10%, preferably from 0.3 to 5%, by weight of the preparation.

The saccharin component of the preparation may be present as saccharin itself or a soluble saccharin salt such as soluble salts which are nontoxic and pharmaceutically acceptable, such as the ammonium, magnesium, calcium or preferably the alkali metal salts, for instance the sodium or potassium salts. It is preferred to use soluble salts of saccharin which are as soluble in water as saccharin itself. Advantageously from 0.01 to 10% (by weight of the preparation) of the saccharin component will be present in the final product, depending on the solubility of the saccharin derivative used. Preferably in solutions for parenteral use this component will be from 0.05 to 1% by weight to volume of solution.

The method in accordance with this invention for making a light-stable phenothiazine preparation comprises mixing a compound containing a phenothiazine nucleus with saccharin or a soluble salt of saccharin using the amounts set forth above and including the other ingredients desirably present in the preparation, for example, a carrier such as water.

The preparations of this invention are illustrated by the following examples of pharmaceutical preparations which are not limiting as to the scope of this invention.

EXAMPLE I

Trifluoperazine Dihydrochloride	0.59# gm.
Sodium Saccharin, U.S.P.	0.13 gm.
Sodium Biphosphate, U.S.P.	0.87 gm.
Sodium Tartrate, Reagent	1.30 gm.
Water for Injection, U.S.P., q.s. ad	100.0 ml.
#Equivalent to 5 mg./ml. of base	

Dissolve the sodium biphosphate and sodium tartrate in 50% of the water, add and dissolve the trifluoperazine dihydrochloride, dissolve the sodium saccharin in 30° portion of the water, add to the buffered drug solution, adjust to final volume with Water for Injection, filter through bacteriological filter, fill into 2 ml. flint ampuls; seal ampuls and autoclave.

EXAMPLE 2

Prochlorperazine Ethanedisulfonate	0.75# gm.
Sodium Saccharin, U.S.P.	0.09 gm.
Sodium Biphosphate, U.S.P.	0.50 gm.
Sodium Tartrate, Reagent	1.20 gm.
Benzyl Alcohol, Reagent	0.75 ml.
Water for Injection, U.S.P., q.s. ad	100.0 ml.
#Equivalent to 5 mg./ml. of base	

Dissolve the benzyl alcohol in 50% of the water, add and dissolve the sodium biphosphate, prochlorperazine ethanedisulfonate and sodium tartrate, dissolve the sodium saccharin in a separate 30% portion of water and add, adjust the final volume to 100.0 ml., filter, fill into 13 ml. amber vials, stopper with black rubber stoppers, seal and autoclave.

EXAMPLE 3

Chlorpromazine Hydrochloride	2.50 gm.
Sodium Saccharin	0.200 gm.
Sodium Sulfite	0.100 gm.
Sodium Bisulfite	0.100 g.m.
Sodium Chloride	0.675 gm.
Ascorbic Acid	0.200 gm.
Water for Injection, q.s. ad	100.0 ml.

Following the general procedures employed in the above examples, the following pharmaceutical preparations are made.

EXAMPLE 4

Trimeprazine Tartrate	3.125 gm.
Sodium Saccharin	0.250 gm.
Sodium Sulfite	0.250 gm.
Tartaric Acid	0.250 gm.
Water for Injection, q.s. ad	100.0 ml.

EXAMPLE 5

Promazine Hydrochloride	4.50 gm.
Sodium Saccharin	1.00 gm.
Sodium Sulfite	0.100 gm.
Sodium Bisulfite	0.100 gm.
Sodium Chloride	0.675 gm.
Ascorbic Acid	0.200 gm.
Water for Injection, q.s. ad	100.0 ml.

EXAMPLE 6

Perphanazine Dihydrochloride	0.65 gm.
Sodium Biphosphate	0.50 gm.
Sodium Tartrate	1.20 gm.
Sodium Saccharin	0.09 gm.
Benzyl Alcohol	0.75 gm.
Water for Injection, q.s. ad	100.0 ml.

EXAMPLE 7

Acetylperphenazine Dihydrochloride	0.71 gm.
(10-[3¹-(N-acetoxyethyl)-piperazinyl-propyl]-2-chlorophenothiazine)	
Sodium Biphosphate	0.87 gm.
Sodium Tartrate	1.30 gm.
Sodium Saccharin	0.13 gm.
Water for Injection, q.s. ad	100.0 ml.

WHAT WE CLAIM IS:—

1. A light-stable phenothiazine preparation comprising a compound containing a phenothiazine nucleus and a stabilizing ingredient comprising saccharin or a soluble salt of saccharin in an amount sufficient to make the phenothiazine nucleus compound substantially stabilized to light.

2. A preparation in accordance with claim 1 characterized in that the stabilizing ingredient is saccharin.

3. A preparation in accordance with claim 1 characterized in that the stabilizing ingredient is a soluble salt of saccharin.

4. A preparation in accordance with any of the preceding claims characterized in that it additionally includes a carrier.

5. A preparation in accordance with claim 4 characterized in that the carrier is water.

6. A preparation in accordance with claim 5 characterized in that the phenothiazine nucleus compound is present in an amount of from 0.1 to 10% by weight and the stabilizing ingredient is present in an amount of from 0.05% to 1% by weight to volume of the preparation.

7. A preparation in accordance with claim 6, characterized in that phenothiazine nucleus compound is a water soluble salt of chlorpromazine, present in an amount of from 0.3 to 5% by weight and the stabilizing ingredient is an alkali metal salt of saccharin.

8. A preparation in accordance with claim 6, characterized in that phenothiazine nucleus compound is a water soluble salt of prochlorperazine, present in an amount of from 0.3% to 5% by weight and the stabilizing ingredient is an alkali metal salt of saccharin.

9. A preparation in accordance with claim 6, characterized in that phenothiazine nucleus compound is a water soluble salt of trifluoperazine, present in an amount of from 0.3% to 5% by weight and the stabilizing ingredient is an alkali metal salt of saccharin.

10. The method of making a phenothiazine nucleus compound substantially stabilized to light which comprises admixing the said compound with a stabilizing ingredient comprising saccharin or a soluble salt of saccharin.

11. The method in accordance with claim 10 characterized in that the stabilizing ingredient is saccharin.

12. The method in accordance with claim 10 characterized in that the stabilizing ingredient is a soluble salt of saccharin.

13. The method in accordance with any of claims 10 to 12 characterized in that the phenothiazine nucleus compound and the stabilizing ingredient are admixed with a carrier.

14. The method in accordance with claim 13 characterized in that the carrier is water.

15. The method in accordance with claim 14 characterized in that the phenothiazine nucleus compound is present in an amount of from 0.1 to 10% by weight and the stabilizing ingredient is present in an amount of from 0.05% to 1% by weight to volume of the preparation.

16. A light-stable phenothiazine preparation comprising a compound containing a phenothiazine nucleus and a stabilizing ingredient comprising saccharin or a soluble salt of saccharin in an amount to make the phenothiazine nucleus compound substantially stabilized to light when produced by the methods described with reference to any of the foregoing examples.

17. A light-stable phenothiazine preparation substantially as hereinbefore described in any one of the foregoing Examples.

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